

CLAIMS

What is claimed is:

1. A peptide which comprises a soluble, trimeric form of a coiled-coil and a sufficient portion of the N-peptide region of HIV gp41 to comprise the amino acid residues which form the pocket of the N-helix coiled-coil of HIV gp41.
2. The peptide of Claim 1 wherein the peptide is a D-peptide.
3. The D-peptide of Claim 2 wherein the coiled coil is selected from the group consisting of:
 - (a) the coiled coil of GCN4-pI_QI;
 - (b) the coiled coil of GCN4-pII;
 - (c) the coiled coil of Moloney Murine Leukemia Virus; and
 - (d) the coiled coil of ABC heterotrimer.
4. The D-peptide of Claim 3 wherein the amino acid sequence of the coiled coil is: RMKQIEDKIEEIESKQKKIENEIARIKK (SEQ ID NO: 25).
5. The D-peptide of Claim 2 wherein the sufficient portion of the N peptide region of HIV gp41 comprises the sequence: LLQLTVWGIKQLQARIL (SEQ ID NO: 20).
6. The D-peptide of Claim 5 which is IQN17 (SEQ ID NO: 2).
7. A D-peptide which is a soluble, trimeric peptide model of the HIV gp41 hydrophobic pocket, wherein the D-peptide comprises SEQ ID NO: 25 and a sequence which comprises 17 amino acid residues, wherein the 17 amino acid

residues comprise the sequence: LLXLTVWGXXXLQXRX (SEQ ID NO: 42), wherein L, T, V, W, G, K, Q and R are amino acid residues represented by the single letter amino acid code and X is any D-amino acid residue.

8. The D-peptide of Claim 7 wherein the sequence which comprises 17 amino acid residues is selected from the group consisting of: SEQ ID NO: 20; SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 42.
9. A D-peptide selected from the group consisting of:
 - (a) CDLKAKEFWWLC (SEQ ID NO: 3);
 - (b) CEARHREWAWLC (SEQ ID NO: 4);
 - (c) CELLGWEWAWLC (SEQ ID NO: 5);
 - (d) CLLRAPEWGWLC (SEQ ID NO: 6);
 - (e) CSRSQPEWEWLC (SEQ ID NO: 7);
 - (f) CGLGQEEFWWLC (SEQ ID NO: 8);
 - (g) CMRGEWEWSWLC (SEQ ID NO: 9);
 - (h) CPPLNKEWAWLC (SEQ ID NO: 10);
 - (i) CVLKAKEFWWLC (SEQ ID NO: 11);
 - (j) KKGACGLGQEEFWWLC (SEQ ID NO: 15);
 - (k) KKGACCELLGWEWAWLC (SEQ ID NO: 16);
 - (l) KKKKGACCELLGWEWAWLC (SEQ ID NO: 17);
 - (m) KKGACMRGEWEWSWLC (SEQ ID NO: 18);
 - (n) KKGACPPPLNKEWAWLC (SEQ ID NO: 19);
 - (o) a D-peptide comprising WXWL (SEQ ID NO: 23);
 - (p) a D-peptide comprising EWXWL (SEQ ID NO: 24);
 - (q) a D-peptide comprising CXXXXXEWXWL (SEQ ID NO: 12)
 - (r) ac-GACEARHREWAWLCAA-am (SEQ ID NO: 34);
 - (r) ac-KKGACEARHREWAWLCAA-am (SEQ ID NO: 38);
 - (t) ac-KKKKGACEARHREWAWLCAA-am (SEQ ID NO: 43);

- (u) ac-GACGLGQEEFWLCAA-am (SEQ ID NO: 44);
- (v) ac-KKGACGLGQEEFWLCAA-am (SEQ ID NO: 15);
- (w) ac-KKKKGACGLGQEEFWLCAA-am (SEQ ID NO: 45)
- (x) ac-GACDLKAKEFWLCAA-am (SEQ ID NO: 35);
- 5 (y) ac-KKGACDLKAKEFWLCAA-am (SEQ ID NO: 39);
- (z) ac-KKKKGACDLKAKEFWLCAA-am (SEQ ID NO: 46);
- (a') ac-GACELLGWEAWLCC-am (SEQ ID NO: 47);
- (b') ac-KKGACELLGWEAWLCAA-am (SEQ ID NO: 16);
- (c') ac-KKKKGACELLGWEAWLCAA-am (SEQ ID NO: 17);
- 10 (d') ac-GACSRSQPEWEWLCAA-am (SEQ ID NO: 36);
- (e') ac-KKGACSRSQPEWEWLCAA-am (SEQ ID NO: 40);
- (f') ac-KKKKGACSRSQPEWEWLCAA-am (SEQ ID NO: 48);
- (g') ac-GACLLRAPEWGWLCAA-am (SEQ ID NO: 37);
- (h') ac-KKGACLLRAPEWGWLCAA-am (SEQ ID NO: 41);
- 15 (i') ac-KKKKGACLLRAPEWGWLCAA-am (SEQ ID NO: 49);
- (j') ac-GACMRGEWEWSWLCAA-am (SEQ ID NO: 50);
- (k') ac-KKGACMRGEWEWSWLCAA-am (SEQ ID NO: 18);
- (l') ac-KKKKGACMRGEWEWSWLCAA-am (SEQ ID NO: 51);
- (m') ac-GACPPLNKEWAWLCAA-am (SEQ ID NO: 52);
- 20 (n') ac-KKGACPPLNKEWAWLCAA-am (SEQ ID NO: 19);
- (o') ac-KKKKGACPPLNKEWAWLCAA-am (SEQ ID NO: 53);
- (p') ac-GACXXXXXEWXWLCAA-am (SEQ ID NO: 54);
- (q') ac-KKGACXXXXXEWXWLCAA-am (SEQ ID NO: 55);
- (r') ac-KKKKGACXXXXXEWXWLCAA-am (SEQ ID NO: 56);
- 25 (s') ac-XXCXXXXXEWXWLCXX-am (SEQ ID NO: 57);
- (t') ac-KKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 58);
- (u') ac-KKKKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 59);
- (v') ac-XXCXXXXXEWXWLCXXX-am (SEQ ID NO: 60);
- (w') ac-KKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 61);

- (x') ac-KKKKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 62); and
 (y') a variant of a sequence of (a) through (x'), wherein the variant binds the N-helix coiled-coil cavity of HIV gp41, wherein ac- at the C-terminus and -am at the N-terminus are optional.

5 10. The peptide of Claim 1 wherein the peptide is an L-peptide.

11. The L-peptide of Claim 10 wherein the soluble, trimeric coiled-coil is selected from the group consisting of:

- (a) the coiled coil of GCN4-pI_QI;
 (b) the coiled coil of GCN4-pII;
 10 (c) the coiled coil of Moloney Murine Leukemia Virus; and
 (d) the coiled coil of ABC heterotrimer.

12. The L-peptide of Claim 10 wherein the sufficient portion of the N peptide region of HIV gp41 comprises the sequence: LLQLTVWGIIKQLQARIL (SEQ ID NO: 20).

15 13. The L-peptide of Claim 12 which is IQN17 (SEQ ID NO: 2).

14. An L-peptide which is a soluble, trimeric model of the HIV gp1 hydrophobic pocket, wherein the L-peptide comprises SEQ ID NO: 25 and a sequence which comprises 17 amino acid residues, wherein the 17 amino acid residues comprise the sequence: LLXLTVWGXXXLQXRXX, wherein L, T, V, W, G, K, Q and R
 20 are amino acid residues represented by the single letter amino acid code and X is any D-amino acid residue.

15. The L-peptide of Claim 14 wherein the sequence which comprises 17 amino acid residues is selected from the group consisting of: SEQ ID NO: 20; SEQ ID NO: 26; and SEQ ID NO: 27.
16. A method of identifying a drug that interferes with formation of a complex between C34 peptide and N36 peptide, comprising:
- 5 (a) combining a candidate drug to be assessed for its ability to interfere with formation of a complex between C34 peptide and N36 peptide, C34 peptide and N36 peptide, under conditions appropriate for formation of a complex between C34 peptide and N36 peptide, thereby forming a test sample; and
- 10 (b) determining whether formation of a complex between C34 peptide and N36 peptide is inhibited,
- wherein if formation of the complex is inhibited, the candidate drug is a drug that interferes with formation of the complex whereby a drug that interferes with formation of the complex is identified.
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17. The method of Claim 16 wherein a control sample is formed by combining C34 peptide and N36 peptide, under the same conditions as the conditions under which the test sample is formed in (a); formation of a complex between C34 peptide and N36 peptide is determined and the extent to which the complex is formed in the test sample is compared with the extent to which the complex is formed in the control sample, wherein if the complex is formed to a lesser extent in the test sample than in the control sample, the candidate drug is a drug that interferes with formation of the complex, whereby a drug that interferes with formation of the complex is identified.
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18. The method of Claim 16 wherein C34 peptide and N36 peptide are each labeled by a member of a pair of donor-acceptor molecules and the extent to which
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formation of a complex between C34 and N36 occurs is assessed by determining the extent to which light emission occurs from the acceptor molecule, wherein if light emission occurs to a lesser extent in the presence of the candidate drug than in the absence of the candidate drug, the candidate drug is a drug that interferes with formation of a complex between C34 peptide and N36 peptide.

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19. The method of Claim 17 wherein C34 peptide and N36 peptide are each labeled by a member of a pair of donor-acceptor molecules and the extent to which light emission occurs is assessed in the test sample and in the control sample, wherein if light emission is less in the test sample than in the control sample, the candidate drug is a drug which inhibits formation of a complex between C34 peptide and N36 peptide.

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20. The method of Claim 16 further comprising assessing whether the drug that interferes with formation of the complex is an inhibitor of HIV entry into cells by assessing the effect of the drug on cell/cell fusion or HIV infection of cells is less in the presence of the drug than in its absence, the drug is an inhibitor of HIV entry into cells.

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21. A method of eliciting an immune response in an individual, comprising introducing into the individual a peptide comprising a trimeric form of a coiled-coil region of a protein and a sufficient portion of the N-peptide region of HIV gp41 to comprise the amino acid residues which form part or all of the N-helix coiled-coil of HIV gp41 and the peptide is present in a pharmaceutically acceptable carrier.

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22. The method of Claim 21 wherein the peptide is introduced into the individual by a route of administration selected from the group consisting of: intramuscularly, intraperitoneally, orally, nasally and transdermally.

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23. The method of Claim 21 wherein the coiled-coil is selected from the group consisting of: GCN4-pI_QI; GCN4-pII; Moloney Murine Leukemia Virus and ABC heterotrimer.
24. The method of Claim 21 wherein the peptide is IQN17.
- 5 25. A method of interfering with entry of HIV into a mucosal cell comprising administering or applying to a mucosal surface a composition comprising: (1) a drug which binds HIV envelope protein gp41 subunit and interferes with entry of HIV into cells of the mucosal surface and (2) a carrier or base.
- 10 26. The method of Claim 25 wherein the drug binds the cavity on the surface of the N-helix coiled-coil of HIV envelope protein gp41 subunit.
27. The method of Claim 26 wherein the drug prevents or reduces the gp41 conformational change, thereby interfering with entry of HIV into cells of the mucosal surface.
- 15 28. The method of Claim 25 wherein the composition comprises a component selected from the group consisting of:
- (a) C34 peptide;
 - (b) DP178;
 - (c) DP649;
 - (d) T1249;
 - 20 (e) a derivative of (a) - (d);
 - (f) a D-peptide which binds to the hydrophobic pocket of HIV gp41;
 - (g) a derivative of (f);
 - (h) a combination of two or more of (a)-(g); and

- (i) a molecule that inhibits HIV infectivity by binding to the N-helix coiled coil.
29. The method of Claim 28 wherein the carrier or base is selected from the group consisting of: a foam, a gel, other substance sufficiently viscous to retain the drug, water and a buffer.
30. The method of Claim 28 wherein the carrier or base is a vaginal suppository or rectal suppository.
31. The method of Claim 28 wherein the drug is released from the carrier or base immediately or soon after it is administered or applied to the vagina, mouth or rectum.
32. The method of Claim 28 wherein the drug is released from the carrier or base gradually or after a specified period after it is administered or applied to the vagina, mouth or rectum.
33. The method of Claim 28 wherein the drug is on the surface of or incorporated within a contraceptive device in a manner which permits release of the drug under conditions of use.
34. The method of Claim 28 wherein the D-peptide of (e) comprises an amino acid sequence selected from the group consisting of:
- (a) CDLKAKEWFWLC (SEQ ID NO: 3);
 - (b) CEARHREWAWLC (SEQ ID NO: 4);
 - (c) CELLGWEWAWLC (SEQ ID NO: 5);
 - (d) CLLRAPEWGWLC (SEQ ID NO: 6);
 - (e) CSRSQPEWEWLC (SEQ ID NO: 7);

- (f) CGLGQEEFWL (SEQ ID NO: 8);
- (g) CMRGEWEWSL (SEQ ID NO: 9);
- (h) CPPLNKEWAWL (SEQ ID NO: 10);
- (i) CVLKAKEFWL (SEQ ID NO: 11);
- 5 (j) KKGACGLGQEEFWL (SEQ ID NO: 15);
- (k) KKGACELLGWEWAWL (SEQ ID NO: 16);
- (l) KKKKGACELLGWEWAWL (SEQ ID NO: 17);
- (m) KKGACMRGEWEWSL (SEQ ID NO: 18);
- (n) KKGACPPLNKEWAWL (SEQ ID NO: 19);
- 10 (o) a D-peptide comprising WXL (SEQ ID NO: 23);
- (p) a D-peptide comprising EXWL (SEQ ID NO: 24);
- (q) a D-peptide comprising CXXXXXEWXL (SEQ ID NO: 12)
- (r) ac-GACEARHREWAWLCAA-am (SEQ ID NO: 34);
- (r) ac-KKGACEARHREWAWLCAA-am (SEQ ID NO: 38);
- 15 (t) ac-KKKKGACEARHREWAWLCAA-am (SEQ ID NO: 43);
- (u) ac-GACGLGQEEFWLCAA-am (SEQ ID NO: 44);
- (v) ac-KKGACGLGQEEFWLCAA-am (SEQ ID NO: 15);
- (w) ac-KKKKGACGLGQEEFWLCAA-am (SEQ ID NO: 45)
- (x) ac-GACDLKAKEFWLCAA-am (SEQ ID NO: 35);
- 20 (y) ac-KKGACDLKAKEFWLCAA-am (SEQ ID NO: 39);
- (z) ac-KKKKGACDLKAKEFWLCAA-am (SEQ ID NO: 46);
- (a') ac-GACELLGWEWAWLCC-am (SEQ ID NO: 47);
- (b') ac-KKGACELLGWEWAWLCAA-am (SEQ ID NO: 16);
- (c') ac-KKKKGACELLGWEWAWLCAA-am (SEQ ID NO: 17);
- 25 (d') ac-GACSRSQPEWEWLCAA-am (SEQ ID NO: 36);
- (e') ac-KKGACSRSQPEWEWLCAA-am (SEQ ID NO: 40);
- (f') ac-KKKKGACSRSQPEWEWLCAA-am (SEQ ID NO: 48);
- (g') ac-GACLLRAPEWGWLCAA-am (SEQ ID NO: 37);
- (h') ac-KKGACLLRAPEWGWLCAA-am (SEQ ID NO: 41);

- (i') ac-KKKKGACLLRAPEWGWLCAA-am (SEQ ID NO: 49);
 (j') ac-GACMRGEWEWSWLCAA-am (SEQ ID NO: 50);
 (k') ac-KKGACMRGEWEWSWLCAA-am (SEQ ID NO: 18);
 (l') ac-KKKKGACMRGEWEWSWLCAA-am (SEQ ID NO: 51);
 5 (m') ac-GACPPLNKEWAWLCAA-am (SEQ ID NO: 52);
 (n') ac-KKGACPPLNKEWAWLCAA-am (SEQ ID NO: 19);
 (o') ac-KKKKGACPPLNKEWAWLCAA-am (SEQ ID NO: 53);
 (p') ac-GACXXXXXEWWLCAA-am (SEQ ID NO: 54);
 (q') ac-KKGACXXXXXEWWLCAA-am (SEQ ID NO: 55);
 10 (r') ac-KKKKGACXXXXXEWWLCAA-am (SEQ ID NO: 56);
 (s') ac-XXCXXXXXEWWLCXX-am (SEQ ID NO: 57);
 (t') ac-KKXXCXXXXXEWWLCXX-am (SEQ ID NO: 58);
 (u') ac-KKKKXXCXXXXXEWWLCXX-am (SEQ ID NO: 59);
 (v') ac-XXCXXXXXEWWLCXXX-am (SEQ ID NO: 60);
 15 (w') ac-KKXXCXXXXXEWWLCXXX-am (SEQ ID NO: 61);
 (x') ac-KKKKXXCXXXXXEWWLCXXX-am (SEQ ID NO: 62); and
 (y') a variant of a sequence of (a) through (x'), wherein the variant binds the
 N-helix coiled-coil cavity of HIV gp41, wherein ac- at the C-terminus
 and -am at the N-terminus are optional.
- 20 35. A method of identifying a compound or molecule which binds the N-helix
 coiled-coil cavity of HIV-1 gp41 envelope protein, wherein the compound or
 molecule to be assessed is referred to as a candidate inhibitor, comprising:
 (a) combining a D-peptide which binds the N-helix coiled-coil cavity, a
 fusion protein which is a soluble model which presents the N-helix
 25 coiled-coil cavity and a candidate inhibitor, under conditions appropriate
 for binding of the D-peptide to the N-helix coiled-coil cavity, thereby
 producing a test sample;

- (b) determining the extent to which binding of the D-peptide to the N-helix coiled-coil cavity in the test sample; and
- (c) comparing the extent of binding determined in to the N-helix coiled-coil cavity in a control sample, wherein the control sample is the same as the test sample except that the control sample does not include the candidate inhibitor and is maintained under the same conditions appropriate for binding of the D-peptide to the N-helix coiled-coil cavity as is the test sample,

wherein if the extent of binding in the test sample is less than the extent of binding in the control sample, the candidate inhibitor is a compound or molecule which binds the N-helix coiled-coil cavity of HIV-1 gp41 envelope protein.

36. The method of Claim 35 wherein the fusion protein is IQN17.

37. The method of Claim 35 wherein the D-peptide is labeled with a fluorescent reporter and the fusion protein is labeled with a quencher which, when in sufficiently close proximity to the fluorescent reporter, quenches the signal from the reporter and detection of a signal from the fluorescent reporter indicates that the candidate inhibitor is a compound or molecule which binds the N-helix coiled-coil cavity of HIV-1 gp41 envelope protein.

38. A fusion protein comprising a trimeric form of the coiled-coil region of GCN4 and a portion of the N-peptide region of HIV-1 gp41, wherein the portion of the N-peptide region of gp41 comprises part or all or none of the N-helix coiled-coil pocket of HIV-1 gp41.

39. A fusion protein of Claim 38 wherein the portion of the N-peptide region of HIV gp41 comprises the following 24 amino acid residues of HIV:

SGIVQQQNNLLRAI EAQQHLLQLT.

40. A method of eliciting an immune response in an individual, comprising introducing into the individual a fusion protein comprising a soluble, trimeric form of a coiled-coil and a sufficient portion of the N-peptide region of HIV-1 gp41, to comprise the amino acid residues which form the pocket of the N-helix coiled-coil of HIV-1 gp41, wherein the fusion protein is present in a pharmaceutically acceptable carrier.
41. A D-peptide which comprises at least four amino acid residues and comprises the consensus sequence WXWL, wherein W represents D-tryptophan, L represents D-leucine and X represents any moiety.
42. The D-peptide of claim 41 wherein X is a D-amino acid residue or a modified D-amino acid residue.
43. The D-peptide of Claim 41, wherein the D-peptide comprises 2 to 21 amino acid residues.
44. A D-peptide which comprises at least five amino acid residues, wherein the at least five amino acid residues are EWXWL, wherein E represents D-glutamic acid, W represents D-tryptophan, L represents D-leucine and X represents an amino acid residue, a modified amino acid residue or a moiety other than an amino acid residue.
45. A D-peptide which comprises an amino acid sequence selected from the group consisting of:
- (a) CDLKAKEWFWLC (SEQ ID NO: 3);
 - (b) CEARHREWAWLC (SEQ ID NO: 4);
 - (c) CELLGWEWAWLC (SEQ ID NO: 5);
 - (d) CLLRAPEWGWLC (SEQ ID NO: 6);

- (e) CSRSQPEWEWLC (SEQ ID NO: 7);
- (f) CGLGQEEFWWLC (SEQ ID NO: 8);
- (g) CMRGWEWSWLC (SEQ ID NO: 9);
- (h) CPPLNKEWAWLC (SEQ ID NO: 10);
- 5 (i) CVLKAKEFWWLC (SEQ ID NO: 11);
- (j) KKGACGLGQEEFWWLC (SEQ ID NO: 15);
- (k) KKGACELLGWEWAWLC (SEQ ID NO: 16);
- (l) KKKKGACELLGWEWAWLC (SEQ ID NO: 17);
- (m) KKGACMRGEWEWSWLC (SEQ ID NO: 18);
- 10 (n) KKGACPLNKEWAWLC (SEQ ID NO: 19);
- (o) a D-peptide comprising WXWL (SEQ ID NO: 23);
- (p) a D-peptide comprising EWXWL (SEQ ID NO: 24);
- (q) a D-peptide comprising CXXXXXEWXWL (SEQ ID NO: 12)
- (r) ac-GACEARHREWAWLCAA-am (SEQ ID NO: 34);
- 15 (r) ac-KKGACEARHREWAWLCAA-am (SEQ ID NO: 38);
- (t) ac-KKKKGACEARHREWAWLCAA-am (SEQ ID NO: 43);
- (u) ac-GACGLGQEEFWLCAA-am (SEQ ID NO: 44);
- (v) ac-KKGACGLGQEEFWLCAA-am (SEQ ID NO: 15);
- (w) ac-KKKKGACGLGQEEFWLCAA-am (SEQ ID NO: 45)
- 20 (x) ac-GACDLKAKEFWWLCAA-am (SEQ ID NO: 35);
- (y) ac-KKGACDLKAKEFWWLCAA-am (SEQ ID NO: 39);
- (z) ac-KKKKGACDLKAKEFWWLCAA-am (SEQ ID NO: 46);
- (a') ac-GACELLGWEWAWLCC-am (SEQ ID NO: 47);
- (b') ac-KKGACELLGWEWAWLCAA-am (SEQ ID NO: 16);
- 25 (c') ac-KKKKGACELLGWEWAWLCAA-am (SEQ ID NO: 17);
- (d') ac-GACRSQPEWEWLCAA-am (SEQ ID NO: 36);
- (e') ac-KKGACRSQPEWEWLCAA-am (SEQ ID NO: 40);
- (f') ac-KKKKGACRSQPEWEWLCAA-am (SEQ ID NO: 48);
- (g') ac-GACLLRAPEWGWLCAA-am (SEQ ID NO: 37);

- 5 (h') ac-KKGACLLRAPEWGWLCAA-am (SEQ ID NO: 41);
(i') ac-KKKKGACLLRAPEWGWLCAA-am (SEQ ID NO: 49);
(j') ac-GACMRGEWEWSWLCAA-am (SEQ ID NO: 50);
(k') ac-KKGACMRGEWEWSWLCAA-am (SEQ ID NO: 18);
(l') ac-KKKKGACMRGEWEWSWLCAA-am (SEQ ID NO: 51);
(m') ac-GACPPLNKEWAWLCAA-am (SEQ ID NO: 52);
(n') ac-KKGACPPLNKEWAWLCAA-am (SEQ ID NO: 19);
(o') ac-KKKKGACPPLNKEWAWLCAA-am (SEQ ID NO: 53);
(p') ac-GACXXXXXEWXWLCAA-am (SEQ ID NO: 54);
10 (q') ac-KKGACXXXXXEWXWLCAA-am (SEQ ID NO: 55);
(r') ac-KKKKGACXXXXXEWXWLCAA-am (SEQ ID NO: 56);
(s') ac-XXCXXXXXEWXWLCXX-am (SEQ ID NO: 57);
(t') ac-KKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 58);
(u') ac-KKKKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 59);
15 (v') ac-XXCXXXXXEWXWLCXXX-am (SEQ ID NO: 60);
(w') ac-KKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 61);
(x') ac-KKKKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 62); and
(y') a variant of a sequence of (a) through (x'), wherein the variant binds the
N-helix coiled-coil cavity of HIV gp41, wherein ac- at the C-terminus
20 and -am at the N-terminus are optional.

46. A method of identifying a drug that binds the N-helix coiled-coil cavity of HIV gp41 comprising:
- 25 (a) combining: (1) a candidate drug to be assessed for its ability to bind the N-helix coiled-coil cavity of HIV gp41 and; (2) a fusion protein which comprises a trimeric version of the coiled-coil region of a protein and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity, under conditions appropriate for presentation of the HIV gp41 cavity for binding by a drug; and

- (b) determining whether the candidate drug binds the HIV gp41 cavity, wherein if binding occurs, the candidate drug is a drug which binds the N-helix coiled-coil cavity of HIV gp41.

47. The method of Claim 46 wherein in (a), a peptide which binds the N-helix coiled-coil cavity of HIV gp41 is combined with the candidate drug and the fusion protein and in (b), whether the candidate drug binds the HIV gp41 cavity is determined in the presence of the peptide which binds the N-helix coiled-coil cavity of HIV gp41.
48. The method of Claim 42 wherein the peptide which binds the N-helix coiled-coil cavity of HIV gp41 is selected from the group consisting of:
- (a) CDLKAKEWFWLC (SEQ ID NO: 3);
 - (b) CEARHREWAWLC (SEQ ID NO: 4);
 - (c) CELLGWEWAWLC (SEQ ID NO: 5);
 - (d) CLLRAPEWGWLC (SEQ ID NO: 6);
 - (e) CSRSQPEWEWLC (SEQ ID NO: 7);
 - (f) CGLGQEEWFWLC (SEQ ID NO: 8);
 - (g) CMRGEWEWSWLC (SEQ ID NO: 9);
 - (h) CPPLNKEWAWLC (SEQ ID NO: 10);
 - (i) CVLKAKEWFWLC (SEQ ID NO: 11);
 - (j) KKGACGLGQEEWFWLC (SEQ ID NO: 15);
 - (k) KKGACELLGWEWAWLC (SEQ ID NO: 16);
 - (l) KKKKGACELLGWEWAWLC (SEQ ID NO: 17);
 - (m) KKGACMRGEWEWSWLC (SEQ ID NO: 18);
 - (n) KKGACPPLNKEWAWLC (SEQ ID NO: 19);
 - (o) a D-peptide comprising WXWL (SEQ ID NO: 23);
 - (p) a D-peptide comprising EWXWL (SEQ ID NO: 24);
 - (q) a D-peptide comprising CXXXXXEWXWL (SEQ ID NO: 12)

- 5 (r) ac-GACEARHREWAWLCAA-am (SEQ ID NO: 34);
 (r) ac-KKGACEARHREWAWLCAA-am (SEQ ID NO: 38);
 (t) ac-KKKKGACEARHREWAWLCAA-am (SEQ ID NO: 43);
 (u) ac-GACGLGQEEFWLCAA-am (SEQ ID NO: 44);
 (v) ac-KKGACGLGQEEFWLCAA-am (SEQ ID NO: 15);
 (w) ac-KKKKGACGLGQEEFWLCAA-am (SEQ ID NO: 45)
 (x) ac-GACDLKAKEFWLCAA-am (SEQ ID NO: 35);
 (y) ac-KKGACDLKAKEFWLCAA-am (SEQ ID NO: 39);
 (z) ac-KKKKGACDLKAKEFWLCAA-am (SEQ ID NO: 46);
- 10 (a') ac-GACELLGWEWAWLCC-am (SEQ ID NO: 47);
 (b') ac-KKGACELLGWEWAWLCAA-am (SEQ ID NO: 16);
 (c') ac-KKKKGACELLGWEWAWLCAA-am (SEQ ID NO: 17);
 (d') ac-GACSRSQPEWEWLCAA-am (SEQ ID NO: 36);
 (e') ac-KKGACSRSQPEWEWLCAA-am (SEQ ID NO: 40);
- 15 (f') ac-KKKKGACSRSQPEWEWLCAA-am (SEQ ID NO: 48);
 (g') ac-GACLLRAPEWGWLCAA-am (SEQ ID NO: 37);
 (h') ac-KKGACLLRAPEWGWLCAA-am (SEQ ID NO: 41);
 (i') ac-KKKKGACLLRAPEWGWLCAA-am (SEQ ID NO: 49);
 (j') ac-GACMRGEWEWSWLCAA-am (SEQ ID NO: 50);
- 20 (k') ac-KKGACMRGEWEWSWLCAA-am (SEQ ID NO: 18);
 (l') ac-KKKKGACMRGEWEWSWLCAA-am (SEQ ID NO: 51);
 (m') ac-GACPPLNKEWAWLCAA-am (SEQ ID NO: 52);
 (n') ac-KKGACPPLNKEWAWLCAA-am (SEQ ID NO: 19);
 (o') ac-KKKKGACPPLNKEWAWLCAA-am (SEQ ID NO: 53);
- 25 (p') ac-GACXXXXXEWXWLCAA-am (SEQ ID NO: 54);
 (q') ac-KKGACXXXXXEWXWLCAA-am (SEQ ID NO: 55);
 (r') ac-KKKKGACXXXXXEWXWLCAA-am (SEQ ID NO: 56);
 (s') ac-XXCXXXXXEWXWLCXX-am (SEQ ID NO: 57);
 (t') ac-KKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 58);

- (u') ac-KKKKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 59);
 (v') ac-XXCXXXXXEWXWLCXXX-am (SEQ ID NO: 60);
 (w') ac-KKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 61);
 (x') ac-KKKKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 62); and
 5 (y') a variant of a sequence of (a) through (x'), wherein the variant binds the N-helix coiled-coil cavity of HIV gp41, wherein ac- at the C-terminus and -am at the N-terminus are optional.
49. The method of Claim 46 wherein the candidate drug is detectably labeled and binding of the candidate drug to the HIV gp41 cavity is determined by detecting
 10 the presence of the detectable label on the HIV gp41 cavity.
50. The method of Claim 46 wherein the fusion protein comprises a soluble, trimeric version of the coiled-coil region of GCN4 and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity.
51. The method of Claim 50 wherein the fusion protein is IQN17 or a variant
 15 thereof, wherein the amino acid sequence of IQN17 is SEQ ID NO.: 2.
52. A method of identifying a drug that binds the N-helix coiled-coil cavity of HIV gp41 comprising:
 (a) combining: (1) a soluble model that presents the N-helix coiled-coil cavity of HIV gp 41 in such a manner that it is available for binding by a
 20 drug and (2) a candidate drug, which is to be assessed for its ability to bind the N-helix coiled-coil cavity; and
 (b) determining whether the candidate drug binds the N-helix coiled coil cavity of the soluble model,
 wherein if binding occurs, the candidate drug is a drug which binds the N-helix
 25 coiled-coil cavity of HIV gp41.

53. A method of producing a drug that binds the N-helix coiled-coil cavity of HIV gp41 and inhibits HIV entry into cells, comprising
- 5 (a) combining (1) a candidate drug to be assessed for its ability to bind the N-helix coiled-coil cavity of HIV gp41 and inhibit HIV entry into cells and (2) a fusion protein which comprises a trimeric version of the coiled-coil region of a protein and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity, under conditions appropriate for presentation of the HIV gp41 cavity for binding by a drug;
- 10 (b) determining whether the candidate drug binds the HIV gp41 cavity, wherein if binding of the candidate drug to the N-helix coiled-coil cavity of HIV gp41, occurs, the candidate *drug* is a drug which binds the N-helix coiled-coil cavity of HIV gp41, whereby a drug which binds the N-helix coiled-coil cavity of HIV gp41 is produced; and
- 15 (c) assessing the ability of the drug produced in (b) to inhibit HIV entry into cells, wherein if the drug inhibits HIV entry into cells, it is a drug which binds the N-helix coiled-coil cavity of HIV gp41 and inhibits HIV entry into cells.
54. The method of Claim 53 wherein the fusion protein of (a)(2) comprises a soluble, trimeric coiled-coil region of GCN4 and a sufficient portion of the
- 20 N-peptide of HIV gp41 to include the HIV gp41 cavity and the ability of the drug produced in (b) to inhibit HIV entry into cells is assessed in a syncytium assay, an infection assay or both.
55. The method of Claim 54 wherein the drug identified in (c) is further assessed for its ability to inhibit HIV entry into cells by *in vivo* assessment in an appropriate
- 25 animal model.

56. The method of Claim 54 wherein the fusion protein is IQN17 or a variant thereof, wherein the amino acid sequence of IQN17 is SEQ ID NO.:2.
57. A method of producing a soluble model of the N-helix coiled-coil cavity of HIV gp41, comprising producing a fusion protein comprising: (a) a soluble, trimeric form of a coiled-coil and (b) a sufficient portion of the N-peptide region of HIV gp41 to comprise the amino acid residues which form the pocket of the N-helix coiled-coil of HIV gp41.
58. The method of Claim 57 wherein the protein of (a) is GCN4-pI_QI, GCN4-pII, Moloney Murine Leukemia Virus or ABC heterotrimer and the sufficient portion of (b) is selected from the group consisting of a portion comprising SEQ ID NO: 20; a portion comprising SEQ ID NO: 26; a portion comprising SEQ ID NO: 27 and a portion comprising SEQ ID NO: 42.
59. The method of Claim 57 wherein the fusion protein is IQN17 or a variant thereof, wherein the amino acid sequence of IQN17 is SEQ ID NO: 2.
60. A method of producing a drug that binds the N-helix coiled-coil cavity of HIV gp41 comprising,
- (a) producing or obtaining a soluble model of the N-helix coiled-coil cavity of HIV gp41;
 - (b) combining: (1) a candidate drug to be assessed for its ability to bind the N-helix coiled-coil cavity of HIV gp41 and (2) the soluble model of the N-helix coiled-coil cavity of HIV gp41; and
 - (c) determining whether the candidate drug binds the N-helix coiled-coil cavity of HIV gp41,
- wherein if the candidate drug binds the N-helix coiled-coil cavity of HIV gp41, the candidate drug is a drug which binds the N-helix coiled-coil cavity of HIV

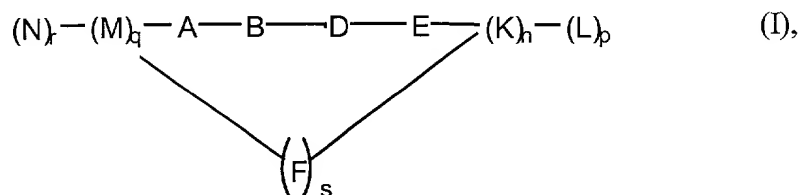
gp41, whereby a drug which binds the N-helix coiled-coil cavity of HIV gp41 is produced.

61. The method of Claim 60 wherein the soluble model is a fusion protein which comprises a trimeric version of the coiled-coil region of a protein and a
5 sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity.
62. The method of Claim 61 wherein the fusion protein is IQN17 or a variant thereof, wherein the amino acid sequence of IQN17 is SEQ ID NO.:2.
63. A method of producing a drug that binds the N-helix coiled-coil cavity of HIV gp41 and inhibits its entry into cells, comprising;
- 10 (a) producing or obtaining a soluble model of the N-helix coiled-coil cavity of HIV gp41;
- (b) combining: (1) a candidate drug to be assessed for its ability to bind the N-helix coiled-coil cavity of HIV gp41 and (2) the soluble model of the N-helix coiled-coil cavity of HIV gp41;
- 15 (c) determining whether the candidate drug binds the N-helix coiled-coil cavity of HIV gp41, wherein if the candidate drug binds the N-helix coiled-coil cavity of HIV gp41, the candidate drug is a drug which binds the N-helix coiled-coil cavity of HIV gp41, whereby a drug which binds the N-helix coiled-coil cavity of HIV gp41 is produced and;
- 20 (d) assessing the ability of the drug produced in (c) to inhibit HIV entry into cells,
- wherein if the drug inhibits HIV entry into cells, it is a drug which binds the N-helix coiled-coil cavity of HIV gp41 and inhibits HIV entry into cells.

64. The method of Claim 63 wherein the soluble model is a fusion protein which comprises a trimeric version of the coiled-coil region of a protein and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity.
65. The method of Claim 64 wherein the fusion protein is IQN17 or a variant thereof, wherein the amino acid sequence of IQN17 is SEQ ID No.;2.
66. A drug produced by the method of Claim 60.
67. A drug produced by the method of Claim 61.
68. A drug produced by the method of Claim 62.
69. A drug produced by the method of Claim 63.
70. A drug produced by the method of Claim 64.
71. A drug produced by the method of Claim 65.
72. A method of identifying a peptide that binds to the N-helix coiled-coil cavity of HIV gp41, comprising:
- (a) combining IQN17 in the D-handedness with a phage display library of L-amino acid peptides, under conditions appropriate for binding of members of the library to IQN17 in the D-handedness; and
 - (b) determining if binding occurs between IQN17 in the D-handedness and a member or members of the phage display library, wherein if binding occurs, a peptide that binds to the N-helix coiled-coil cavity of HIV gp41 in the D-handedness is identified.

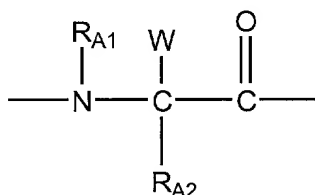
73. The method of Claim 72 further comprising determining the amino acid sequence of the member or members of the phage display library which bind to IQN17 in the D-handedness and producing peptides, in D form, comprising the amino acid sequences determined, wherein the peptides in D form bind the N-helix coiled-coil cavity in the natural L-handedness.

74. A compound of Formula I,



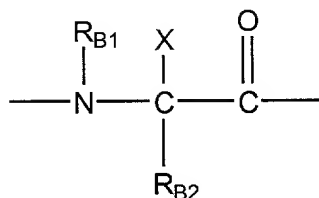
wherein

A is a D- amino acid residue or an N-substituted glycyl residue of the formula



wherein one of R_{A1} and R_{A2} is a substituted or unsubstituted aryl, heteroaryl, arylmethyl, heteroarylmethyl, benzo-fused aryl, benzo-fused heteroaryl, benzo-fused arylmethyl, benzo-fused heteroarylmethyl, cycloalkyl or bicycloalkyl; and the other is hydrogen; and W is hydrogen, methyl, trifluoromethyl or halogen, for example, fluorine, chlorine, bromine or iodine;

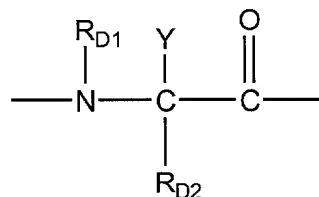
B is a glycyl residue or a D-amino acid or N-substituted glycyl residue of the formula



5

wherein one of R_{B1} and R_{B2} is a substituted or unsubstituted linear, branched or cyclic alkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group; and the other is hydrogen; and X is hydrogen, methyl, trifluoromethyl or halogen, such as fluorine, chlorine, bromine or iodine;

D is a D- amino acid residue or N-substituted glycyl residue of the formula



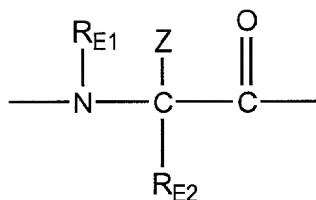
10

wherein one of R_{D1} and R_{D2} is a substituted or unsubstituted aryl, heteroaryl, arylmethyl, heteroarylmethyl, benzo-fused aryl, benzo-fused heteroaryl, benzo-fused arylmethyl; benzo-fused heteroarylmethyl, cycloalkyl or bicycloalkyl; and the other is hydrogen; and Y is hydrogen, methyl, trifluoromethyl or halogen, such as fluorine, chlorine, bromine or iodine;

15

E is a D-amino acid residue or N-substituted glycyl residue of the formula

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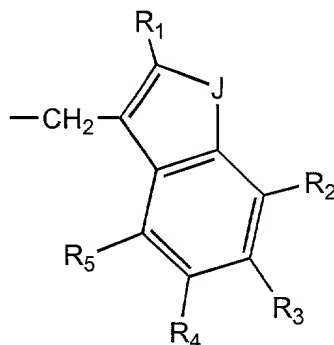
- 5 wherein one of $\text{R}_{\text{E}1}$ and $\text{R}_{\text{E}2}$ is a substituted or unsubstituted, linear, branched or cyclic alkyl, aryl or arylalkyl group; and the other is hydrogen; and Z is hydrogen, methyl, trifluoromethyl or halogen, such as fluorine, chlorine, bromine or iodine;

K, L, M and N are each, independently, an amino acid residue or a polypeptide group comprising 2 to about 8 amino acid residues;

F is a direct bond or a difunctional linking group; and

n, p, q, r and s are each, independently, 0 or 1.

- 10 75. The compound of Claim 74 wherein one of $\text{R}_{\text{A}1}$ and $\text{R}_{\text{A}2}$ and one of $\text{R}_{\text{D}1}$ and $\text{R}_{\text{D}2}$ are, independently, a phenyl, substituted phenyl, naphthyl, substituted naphthyl, naphthylmethyl, substituted naphthylmethyl, benzyl or substituted benzyl group, or a group of the formula



where J is O, S or NR, where R is H or linear, branched or cyclic C₁-C₆-alkyl; and

R₁, R₂, R₃, R₄ and R₅ are independently selected from the group
 5 consisting of

hydrogen, halogen and alkyl.

76. The compound of Claim 75 wherein R_{A1} and R_{D1} are both hydrogen.

77. The compound of Claim 74 wherein one of R_{B1} and R_{B2} is hydrogen, substituted
 10 or unsubstituted linear, branched or cyclic C₁-C₄-alkyl, phenyl, benzyl, naphthyl
 or naphthylmethyl.

78. The compound of Claim 77 wherein R_{B1} is hydrogen.

79. The compound of Claim 74 wherein one of R_{E1} and R_{E2} is a substituted or
 unsubstituted, linear, branched or cyclic C₁-C₆-alkyl group or a substituted or
 unsubstituted phenyl or naphthyl group and the other is hydrogen.

15 80. The compound of Claim 79 wherein R_{E1} is hydrogen.

81. The compound of Claim 74 wherein A and D are each a D-tryptophan residue
 and E is a D-leucine residue.

82. The compound of Claim 74 wherein K is a D-amino acid residue or an N-
 substituted glycyl residue comprising an amino-, carboxyl- or sulfhydryl
 20 substituted side chain and L is a polypeptide comprising 2 or 3 D-amino acid
 residues or N-substituted glycine residues.

83. The compound of Claim 74 wherein M is a polypeptide group comprising from 2 to about 8 D-amino acid residues, of which at least one comprises an amino-, carboxy- or sulfhydryl substituted side chain, and N is a polypeptide group comprising from 1 to about 6 amino acid residues, of which at least one is a lysine residue.
84. The compound of Claim 74 wherein F is a divalent linking group having a length from about 2 to about 40 atoms.
85. The compound of Claim 84 wherein F is a polypeptide linking group of the formula $-P_n-$, wherein n is an integer from 1 to about 12 and each P is independently an L- or D- amino acid or N-substituted glycyl residue, a glycyl residue or an N-substituted glycyl residue.
86. The compound of Claim 84 wherein F is a substituted or unsubstituted C_4-C_{40} -alkylene group or a C_4-C_{40} -alkylene group which is interrupted at one or more points by a heteroatom, a phenylene group or a heteroarylene group.
87. The compound of Claim 84 wherein F is a polysaccharide group comprising from 1 to about 10 glycoside groups.
88. A method of producing a drug which fits the N-helix coiled-coil pocket of HIV gp41, comprising:
- (a) obtaining a crystal of a soluble, trimeric peptide model of the HIV gp41 hydrophobic pocket;
 - (b) obtaining the atomic coordinates of the peptide model by X-ray diffraction studies using the crystal obtained in (a);
 - (c) using the atomic coordinates obtained in (b) to define the N-helix coiled-coil pocket of HIV gp41;

- (d) identifying a molecule or compound which fits the N-helix coiled-coil pocket of HIV gp41;
- (e) obtaining the molecule or compound identified in (d); and
- (f) contacting the molecule or compound obtained in (e) with the N-helix coiled-coil pocket of HIV gp41 to assess the ability of the molecule or compound to fit the pocket of HIV gp41,

wherein if the molecule or compound fits the N-helix coiled-coil pocket of HIV gp41, the molecule or compound is a drug which fits the pocket, whereby a drug which fits the N-helix coiled-coil pocket of HIV gp41 is produced.

- 10 89. The method of Claim 88 wherein the soluble, trimeric peptide molecule comprises a soluble, trimeric form of a coiled coil and a sufficient portion of the N-peptide region of HIV gp41 to comprise the amino acid residues which form the pocket of the N-helix coiled-coil of HIV gp41.
- 15 90. The method of Claim 89 wherein in (f), the molecule or compound is contacted with the N-helix coiled-coil pocket of HIV gp41 by contacting the molecule or compound with IQN17, the N-helix of HIV gp41 or a polypeptide which comprises the HIV pocket.
91. The method of Claim 89 wherein the soluble model is IQN17.
- 20 92. The method of Claim 88 wherein the crystal obtained in (a) is a crystal of IQN17 of space group C222.
93. A method of producing a drug which binds the N-helix coiled-coil pocket of HIV gp41, comprising:
- (a) obtaining the atomic coordinates of IQN17;

- (b) using the atomic coordinates obtained in (a) to define the N-helix coiled-coil pocket of HIV gp41;
- (c) identifying a molecule or compound which fits the N-helix coiled-coil pocket of HIV gp41;
- 5 (d) obtaining the molecule or compound identified in (c); and
- (e) contacting the molecule or compound obtained in (d) with the N-helix coiled-coil pocket of HIV gp41 to assess the ability of the molecule or compound to fit the pocket of HIV gp41,
- wherein if the molecule or compound fits the N-helix coiled-coil pocket of HIV gp41, the molecule or compound is a drug which fits the pocket, whereby a drug which fits the N-helix coiled-coil pocket of HIV gp41 is produced.
- 10
94. The method of Claim 93 wherein the atomic coordinates are the atomic coordinates in the PDB file represented in Figures 11A-11V.
95. A method of identifying a molecule that binds to the N-helix coiled-coil cavity of HIV gp41, comprising:
- 15 (a) combining IQN17 in the D-handedness with a biologically encoded library of ligands, under conditions appropriate for binding of members of the library to IQN17 in the D-handedness; and
- (b) determining if binding occurs between IQN17 in the D-handedness and a member or members of the biologically encoded library, wherein if binding occurs, a ligand that binds to the N-helix coiled-coil cavity of HIV gp41 in the D-handedness is identified.
- 20
96. The method of Claim 95 further comprising determining the sequence of the member or members of the biologically encoded library which bind to IQN17 in the D-handedness, and producing ligands, in the mirror-image handedness of the biologically encoded ligands, comprising the sequences determined.
- 25

97. The method of Claim 95 wherein the biologically encoded library is selected from the group consisting of a phage display library, a DNA library, an RNA library and a biologically encoded peptide library.